Lithium Use in Pregnancy and the Risk of Cardiac Malformations

TO THE EDITOR: Patorno et al. (June 8 issue)[1] provided information on the risk of cardiac malformation in infants exposed to lithium during the first trimester of pregnancy. The risk is higher than in nonexposed infants or in infants exposed to lamotrigine, but the association is of a smaller magnitude than previously reported.

We emphasize that these findings do not imply or support the idea that lithium treatment should be discontinued in women who are pregnant or planning a pregnancy or that lithium treatment should be avoided in women of childbearing age. If properly managed, lithium is the most effective prophylactic treatment option for bipolar disorder, both in and outside the perinatal period, and it has a side-effect profile that is more favorable than usually assumed.[2,3] The increased risk of cardiac malformation presented in this research needs to be weighed against the high risk of a postpartum recurrence of bipolar disorder in women who do not receive treatment (in a recent meta-analysis, the risk was found to be 66% [95% confidence interval, 57 to 75][4]), as well as against the risks associated with alternative perinatal treatment options, such as lamotrigine[3] or the combined use of antipsychotics and antidepressants.[5]

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TO THE EDITOR: The article by Patorno et al. on the relationship between maternal lithium use and the risk of congenital cardiac malformations is difficult to interpret because of the incorrect identification of Ebstein's anomaly, which has previously been linked to lithium use during pregnancy. Ebstein's anomaly is distinctly not a form of right ventricular outflow obstruction. It involves the inflow portion of the right ventricle, not the outflow tract, and results in valvular insufficiency, not obstruction. No clinician would classify right ventricular outflow obstruction as Ebstein's anomaly because of maternal lithium use. Although Ebstein's anomaly is occasionally associated with pulmonary stenosis or atresia, these are exceptions.

Thus, it is not possible to determine whether lithium exposure is associated with Ebstein's anomaly. The authors state that none of the right ventricular outflow tract lesions were specifically coded as Ebstein's anomaly. I hope not, because these are entirely different malformations.

The article does provide reassurance that the risk associated with maternal lithium use is probably lower than previously thought and seems to be present only when large doses of the medication are used.

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THE AUTHORS REPLY: Di Florio et al. emphasize the important point that patients and clinicians need to balance the increased risk of cardiac malformations we found in our study and the benefits of lithium for treating bipolar disorder in women who are pregnant or who may potentially become pregnant.[1,2]

Gutgesell clarifies the anatomical characteristics of Ebstein's anomaly and gives us the opportunity to justify the classification scheme we used in our analyses. We examined the effect of lithium exposure on three different end points related to cardiac malformations: cardiac malformations overall (primary outcome), right ventricular outflow (and inflow) tract defects, and Ebstein's anomaly. We combined right heart defects, as had been done in other epidemiologic studies, because these defects might be pathogenetically related.[3] The wide net that was cast in the first two levels of analysis aimed to capture any potential less specific effects of lithium on cardiac malformations. However, it is important to note that we also evaluated Ebstein's anomaly specifically and found none in the 663 pregnancies with lithium exposure. As Gutgesell concludes, this finding provides reassurance, since the initially proposed relative risk of 400 from the uncontrolled International Register of Lithium Babies[2,4] would have predicted approximately 15 cases of Ebstein's anomaly, given a baseline prevalence of 5 cases per 100,000 births.[5] Our findings further suggest a much more modest association of lithium exposure, particularly at lower doses, with cardiac defects overall and with right heart defects considered as a composite group.

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Since publication of their article, the authors report no further potential conflict of interest.

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Myeloproliferative Neoplasms

TO THE EDITOR: In his article on myeloproliferative neoplasms, Spivak (June 1 issue)[1] briefly addresses the diagnostic effect of morphologic features and states that "bone marrow histologic features cannot provide specificity, except that myelodysplasia can be ruled out on the basis of histologic features." The author completely disregards the World Health Organization (WHO) classification of myeloproliferative neoplasms, particularly the advancements introduced in the 2016 revision.[2] Specifically, Spivak did not mention the bone marrow biopsy characteristics and the associated clinical effects of early-stage polycythemia vera[3] or the clinical relevance of prefibrotic myelofibrosis and its differentiation from essential thrombocythemia.[4] Until now, none of the various molecular mutations have proven to be specific and therefore cannot be applied to the molecular classification of myeloproliferative neoplasms or used to distinguish essential thrombocythemia from prefibrotic myelofibrosis. The so-called transformation of myeloproliferative neoplasms, erroneously assumed by the author to make diagnosis a moving target — with essential thrombocythemia (i.e., early polycythemia vera) progressing to overt polycythemia vera or essential thrombocythemia (i.e., prefibrotic myelofibrosis progressing to myelofibrosis) — is actually related to the accuracy of the initial diagnosis.[5]

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